

YEAR IN CARDIOLOGY SERIES**The Year in Valvular Heart Disease**

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This review includes articles published from July 2002 to June 2003, with three exceptions.

AORTIC STENOSIS

Percutaneous transcatheter prosthetic heart valve (PHV) insertion. The first human implantation of an aortic PHV was performed by the percutaneous transcatheter technique (1). This was a “last resort” procedure in a patient with severe calcific aortic stenosis (AS) (aortic valve area [AVA] 0.6 cm²; left ventricular ejection fraction [LVEF] 0.14), cardiogenic shock, and a multitude of co-morbid conditions. The PHV area was 1.6 cm², and paravalvular aortic regurgitation (AR) was mild. The patient died 17 weeks later from the associated co-morbid conditions (Fig. 1).

COMMENT. In humans, transcatheter PHV had been implanted previously in the pulmonary position (2), and a report of a larger series is in press in *JACC*.

Calcific AS: pathogenesis. A number of reports provided evidence that the pathogenesis of AS is an active process having many similarities to atherosclerosis.

- a) Rabbits fed a cholesterol diet by Rajamannan et al. (3) revealed an increase of blood cholesterol and high sensitive C-reactive protein (hsCRP) levels. Their aortic valve (AV) showed increases of proliferation cell nuclear antigen (PCNA), macrophages (RAM 11), and osteoblast bone markers [alkaline phosphatase, osteopontin, and osteoblast lineage-specific transcription factor (Cbfa-1)], which were absent in the control animals fed a normal diet. A third group of animals fed a cholesterol diet plus atorvastatin had a reduction of all the above markers except hsCRP (Fig. 2).
- b) These same investigators then examined stenotic AV resected at time of aortic valve replacement (AVR) and normal human AV removed at time of cardiac transplantation (4). They documented the presence of calcification and of CaPO₄ in the AS valves. Reverse transcriptase-polymerase chain reaction revealed increased mRNA levels of osteopontin, bone sialoprotein, osteocalcin, and osteoblast-specific transcription factor Cbfa1 in the calcified valves. They confirmed their hypothesis, namely that AV calcification is *not* a

random degenerative process but an active regulated process associated with an osteoblast-like phenotype.

- c) In another experimental study, the addition of vitamin D₂ to the cholesterol-enriched diet was necessary to produce AS (5).
- d) Studies of calcific AS identified high levels of TGF-β₁ in calcified valve nodules, which stimulated AV interstitial cell in culture to aggregate, induce cellular apoptosis, and calcify (6).
- e) Patients who had AVR for severe AS when compared to age- and gender-matched controls had higher levels of lipoprotein (a), *Chlamydia pneumoniae*, IgG antibody titers, high plasma leptin, and tissue-type plasminogen activator mass concentration (7).
- f) T-lymphocyte infiltration was present in tricuspid and bicuspid AV without any significant difference in extent and localization (8). Inflammation should be considered in the pathogenesis of AS in both types of valves.
- g) The suggested steps involved in the development of calcific AS are summarized in Figure 3 (9).

COMMENT. The term “degenerative” as the etiology of calcific AS needs to be abandoned.

Hypertrophy and failure in AS: structural findings. Structural abnormalities were studied in left ventricular (LV) myectomies from three groups of patients with severe AS undergoing AVR (group 1, LVEF >50%, n = 12; group 2, LVEF 30% to 50%, n = 12; group 3, LVEF <30%, n = 10) and six control patients with mitral stenosis (MS) (group 4, LVEF 61 ± 8%) (10). Myocyte hypertrophy was accompanied by increased nuclear deoxyribonucleic acid and Sc-35 (splicing factor) content. In the three groups, angiotensin-converting enzyme (ACE) inhibitor and TGF-β₁ were up-regulated with fibrosis, which increased by 2.3, 2.2, and 3.2 times over control; myocyte degeneration increased by 10, 22, and 32 times over control (Fig. 4); ubiquitin-related autophagic cell death was 0.5%, 1.05%, and 6.05%; death by oncosis was 3%, about 5%, and 4%, respectively. Apoptosis was 0.2% in group 1, and 0.01% in group 2, but was not seen in groups 3 and 4. Cardiomyocyte mitosis was not observed. The investigators suggested a model of major adaptation to pressure overload (Fig. 5).

COMMENT. The *r* values of various correlations were only 0.58, 0.57, and 0.65; it is possible that endocarditis (which was the etiology in 65% of patients) and its duration had a role in the observed findings.

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Manuscript received October 31, 2003; accepted December 3, 2003.

Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
AR	= aortic regurgitation
AS	= aortic stenosis
AVA	= aortic valve area
AVR	= aortic valve replacement
CAD	= coronary artery disease
CBC	= catheter balloon commissurotomy
CO	= cardiac output
LA	= left atrial/atrium
LV	= left ventricular/ventricle
LVEF	= left ventricular ejection fraction
LVSWL	= left ventricular stroke work loss
MR	= mitral regurgitation
MS	= mitral stenosis
MVA	= mitral valve area
MV _{rep}	= mitral valve repair
NYHA	= New York Heart Association
OMC	= open mitral commissurotomy
OR	= odds ratio
PHV	= prosthetic heart valve
PHVT	= prosthetic heart valve thrombosis
SVD	= structural valve deterioration
TEHV	= tissue-engineered heart valve
V _O ₂	= body oxygen consumption

Assessment of severity. The calculation of energy loss co-efficient (ELCO) by echocardiography/Doppler provided assessment of severity of AS, which was similar to that obtained by calculating AVA from data obtained at cardiac catheterization (Fig. 6) (11). Table 1 shows the theoretical Doppler-derived AVA at different aortic cross-sectional areas to “catheter-derived” AVA.

COMMENT. The best correlation is from patients who had AVAs $\leq 1.0 \text{ cm}^2$ (Fig. 6); theoretically derived AVA needs confirmation in man (Table 1).

Another study compared various indices obtained from echocardiography/Doppler assessments to patient outcomes. The LV stroke work loss (LVSWL) was calculated as $AP (AP + SBP) \times 100$, where AP was the mean aortic gradient and SBP (systolic blood pressure) were determined

in the echocardiographic laboratory (12). An LVSWL of $>25\%$ best discriminated clinical end points.

COMMENT. The concept of LVSWL as a parameter for assessment of severity of AS was conceived and developed by John R. Tobin Jr. (13). It stated that the pressure-volume work lost in imparting kinetic energy to allow LV emptying had to relate to severity of AS and proved it to be correct with planimeted LV and aortic systolic pressures obtained at cardiac catheterization. The present study has importantly extended this observation to determine the relationship of LVSWL to patient outcomes and to show it to be better than all the other parameters even though the determination of LVSWL was less than ideal.

Specific clinical syndromes. HEYDE'S SYNDROME. This syndrome involves bleeding from gastrointestinal dysplasia in patients with severe AS in whom bleeding usually ceases after AVR. Two women who had bleeding from endoscopically proven dysplasia (14) had severe deficiency of high-molecular-weight multimers of von Willebrand factor, which normalized postoperatively. Up to 10 years' postoperation, neither patient had recurrent bleeding or anemia or required iron supplements.

EVALUATION OF NITROPRUSSIDE IN CRITICALLY ILL PATIENTS. A total of 25 patients, mean age 73 ± 15 years, with severe AS ($AVA \leq 1.0 \text{ cm}^2$), $LVEF \leq 0.35$, and cardiac index $\leq 2.2 \text{ l/min/m}^2$ received intravenous nitroprusside in a dose titrated to produce a mean arterial pressure between 60 and 70 mm Hg (15). The *primary end point of the study* was change from baseline in the cardiac index during nitroprusside administration for 24 h. At 24 h, the cardiac index had increased from 1.60 ± 0.35 to $2.52 \pm 0.55 \text{ l/min/m}^2$. However, mean arterial pressure also *decreased* from 81 to 69 and mean pulmonary artery (PA) wedge pressure fell from 27 to only 23. All patients continued to receive nitroprusside until conversion to conventional medical therapy, death, or surgery (in some patients many days later). The AVR was performed in 21 patients (one died), coronary artery bypass graft (CABG)

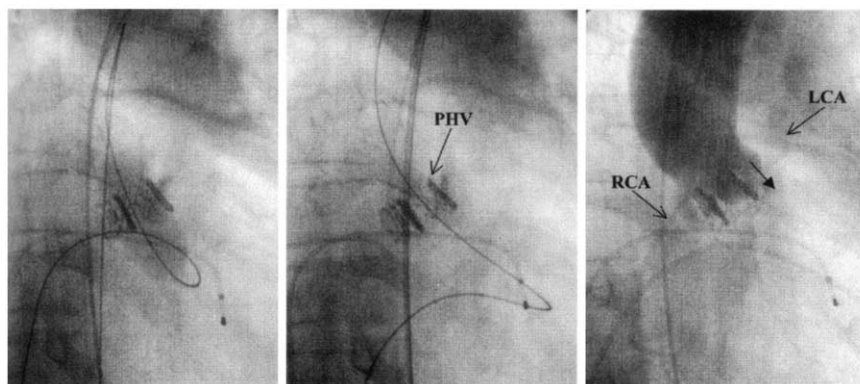


Figure 1. Percutaneous catheter implantation aortic valve replacement via the transeptal route. Aortogram in **right panel** shows no aortic regurgitation from prosthetic heart valve (PHV) but mild paravalvular regurgitation (arrow). LCA = left coronary artery; RCA = right coronary artery. (From Cribier A, et al., ref. 1.)

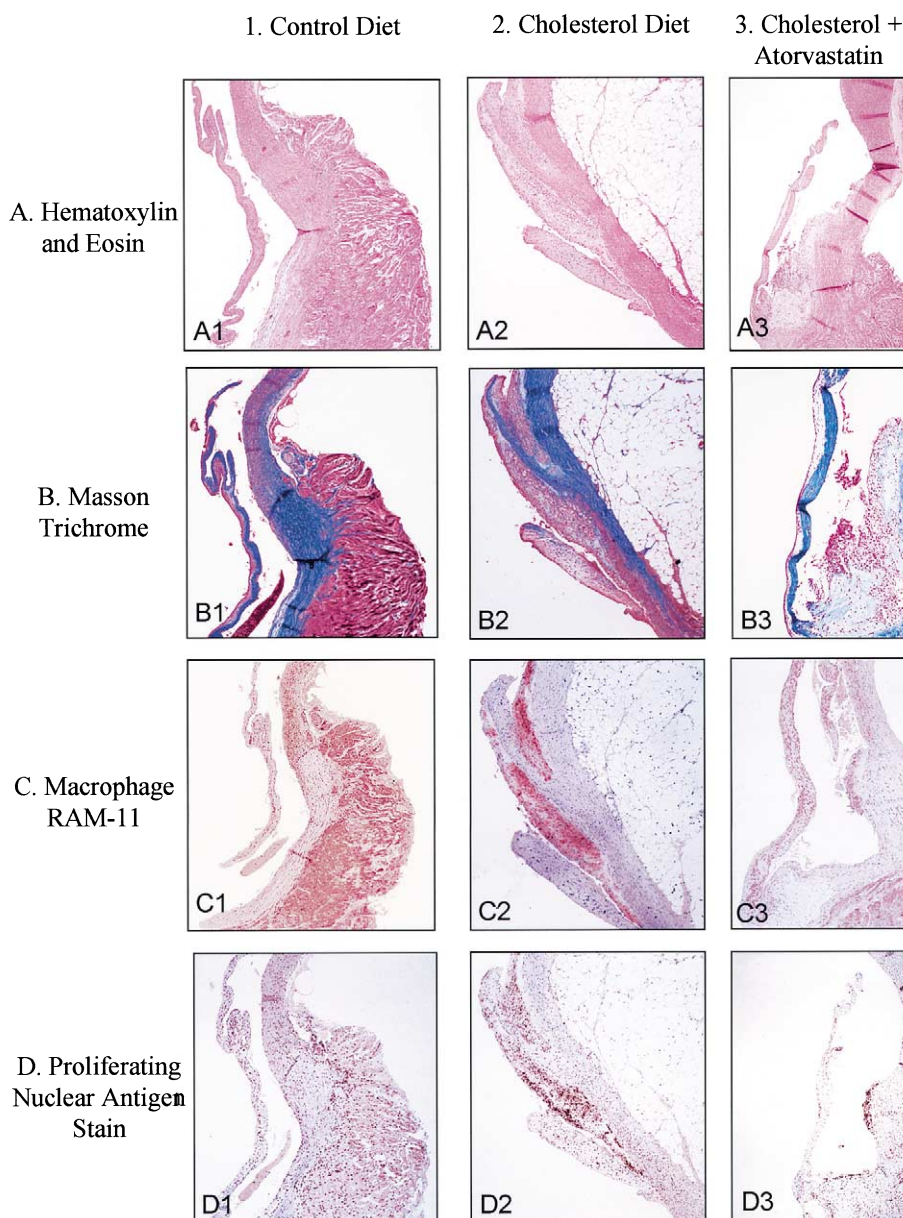


Figure 2. The normal aortic valve surface is thin and intact, with a smooth endothelial layer in the spongiosa layer of the valve (**A1, B1**) and there are no macrophages or proliferation (**C1, D1**). On a cholesterol diet, foam cells converged to form a large lipid-laden lesion on the valve leaflet (**A2**), collagen is formed and is stained blue (**B2**), foam cells stained positive for macrophage (**C2**), and there is a marked increase in myofibroblast proliferation cell nuclear antigen staining (**D2**). Animals on a cholesterol diet and treated with atorvastatin had a marked decrease (**A3–D3**) in the abnormal findings seen in animals on only the cholesterol diet (**A2–D2**). (From Rajamannan NM, et al., ref. 3.) Prints of the figure were provided by Dr. Rajamannan.

without AVR in 1, balloon valvuloplasty in 1, and medical therapy in the remaining patients. There were five in-hospital deaths; at 30 days, the survival rate was 76%. The investigators concluded that nitroprusside could be used effectively in severe AS.

COMMENT The concerns are: 1) The single most important goal and primary end point was an increase in cardiac index (measured by the Fick principle). However, the body oxygen consumption ($\dot{V}O_2$) for calculation of cardiac output (CO) was *not measured* (G. Francis, personal communication, July

7, 2003; copy of letter submitted to Editor in Chief) but was obtained from a nomogram of $\dot{V}O_2$ of “normal” people at rest, which is probably not accurate for those in heart failure and also may not be the same before and after nitroprusside. As a consequence, all calculated values of CO, stroke volume, and systemic vascular resistance are suspect. 2) There was only a small reduction of PA wedge pressure. 3) Patients were *not* given diuretics or digitalis but were given beta-blockers. 4) Mean arterial pressure was reduced. 5) The numbers of patients who had coronary arteriography

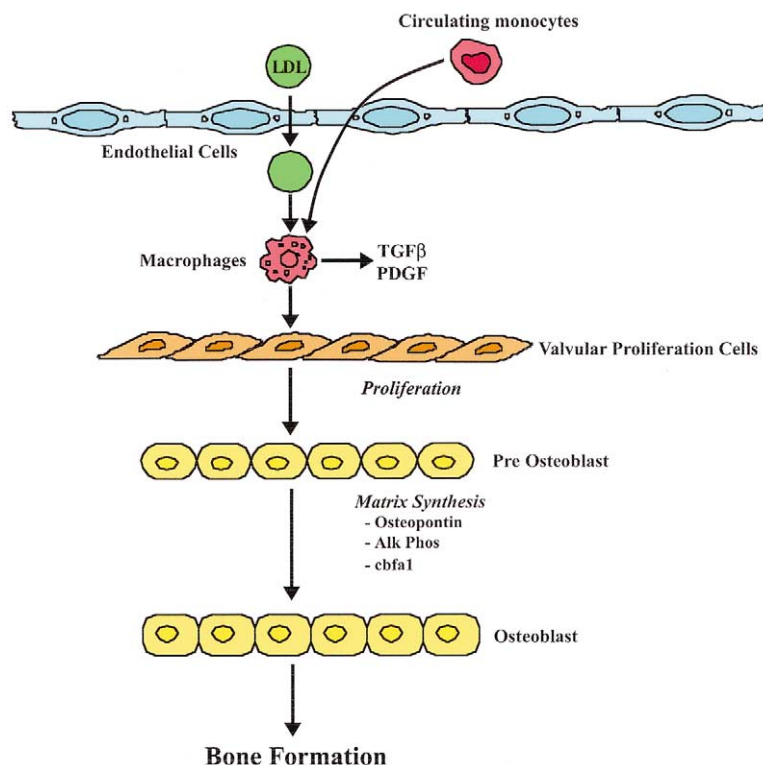


Figure 3. Possible mechanism for the development of aortic valve calcification. The cell within the valve develops osteoblast-like features that synthesize important bone matrix proteins involved in the calcification process in the valve. (From Rajamannan NM, et al., ref. 4.) Prints of the figure were provided by Dr. Rajamannan.

and had significant obstructive coronary artery disease (CAD) were not provided. In this age group, $\geq 50\%$ of patients can be expected to have associated CAD.

LOW GRADIENT AORTIC STENOSIS WITH DEPRESSED LV SYSTOLIC FUNCTION. To determine the severity of valve obstruction in low gradient AS with depressed LV systolic function, selected patients with echocardiographic/Doppler AVA $<1.0 \text{ cm}^2$, mean AV gradient $<40 \text{ mm Hg}$, and LVEF <0.40 underwent dobutamine infusion in the cardiac catheterization laboratory (16). Twenty-one patients had AVR, and their outcome was evaluated in two subgroups on basis of an increase of stroke volume of $\geq 20\%$ ("contractile reserve"). Following AVR, 12 of 15 patients (80%) with "contractile reserve" were in New York Heart Association (NYHA) functional class I and II; 2 of 6 (33%) without "contractile reserve" were in NYHA functional class I and II.

The investigators concluded: "In patients with left ventricular systolic dysfunction and aortic stenosis with a low output and low mean gradient, dobutamine challenge *may* aid in selecting those who would benefit from an aortic valve operation."

COMMENT. It is questionable whether changes in stroke volume should be labeled as an index of contractility. Decisions for AVR were made by individual clinicians, and one patient with "mild" AS had AVR. This was an elegant study in the catheterization laboratory. This study (16)

shows that the cause(s) of this clinical syndrome is multifactorial because of baseline patient characteristics such as hypertension, very high left atrial (LA) pressure, mitral regurgitation (MR), and other factors. For example: 1) the patient shown in the investigators' Figure 2A (16) was very hypertensive, and dobutamine produced a decline in arterial pressure and a marked increase in CO; 2) the patient in Figure 2B: with dobutamine there was a marked increase in arterial and LV pressure with little increase of CO; and 3) the patient in Figure 2C had very high LV end-diastolic pressure, high LA pressure with marked "v" waves, which increased further with dobutamine. This study shows dobutamine may have complex effects, and the findings of changes in mean aortic valve gradient, and perhaps even in AVA, may be misleading if all the hemodynamic data are not carefully analyzed in detail.

SEVERE AORTIC STENOSIS WITH SEVERE PULMONARY HYPERTENSION (PHTN). A total of 37 patients with severe AS (AVA $\leq 1.0 \text{ cm}^2$) had severe PHTN (Doppler systolic pressure 78.8) of whom 86% underwent AVR (17). The operative mortality was 16% and the five-year survival was 48%, which is most encouraging, but their survival rates are compared only to age- and gender-matched patients in the population.

COMMENT. This is a small but important subgroup of patients with severe AS. The data in patients who underwent AVR are important and interesting (18), but compar-

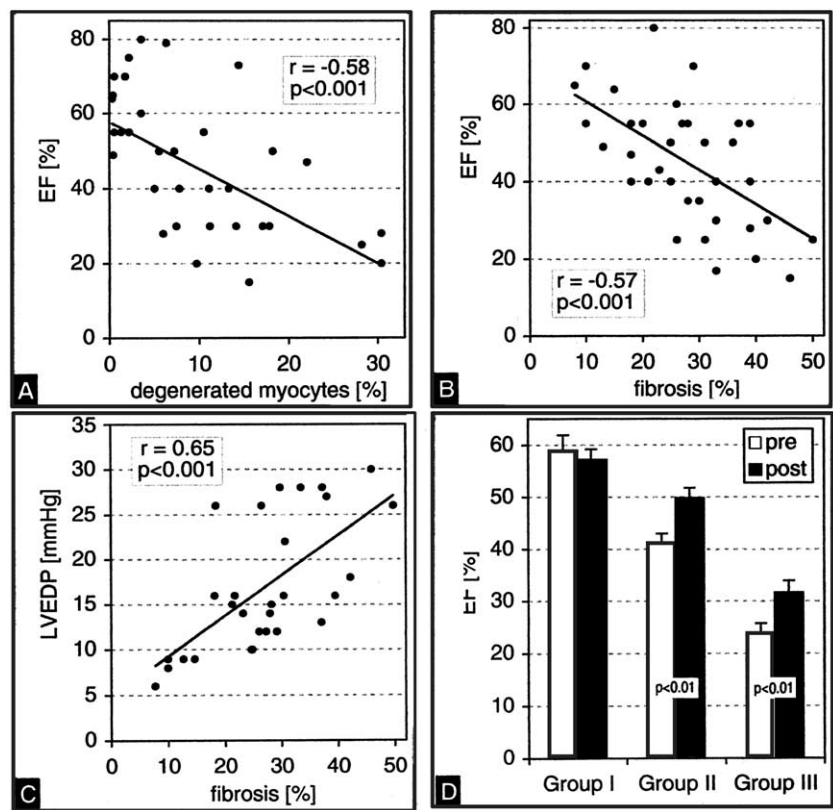


Figure 4. Shown are the relationships between degenerated myocytes and left ventricular ejection fraction (EF) (A), fibrosis and left ventricular EF (B), fibrosis and left ventricular end-diastolic pressure (LVEDP) (C), and changes in left ventricular EF after aortic valve replacement (D) in the three groups of patients. (From Hein S, et al., ref. 10.)

ison to the population is of dubious clinical value. It is not obvious why 10 patients did not have AVR; many probably had the phenomenon of “excessive hypertrophy” (19). Not performing coronary arteriography is called “reasonable” (20); however, considering the patients’ ages and associated risk factors it is highly likely $\geq 50\%$ of patients may have had significant CAD. Severe AS \pm CAD may have caused

severe LV diastolic dysfunction. With AVR \pm CABG, many could have had a “good” outcome. Note that they had severe AS plus normal or good LVEF. Important question: was survival statistically significantly better with AVR \pm

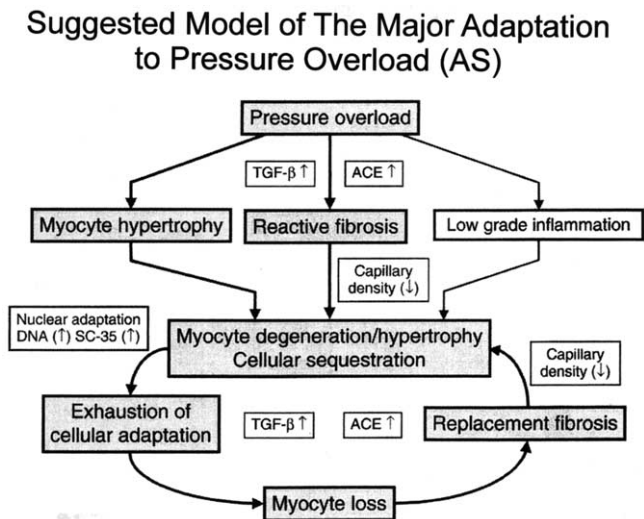


Figure 5. A suggested pathway from hypertrophy to failure in AS \pm endocarditis. (From Hein S, et al., ref. 10.)

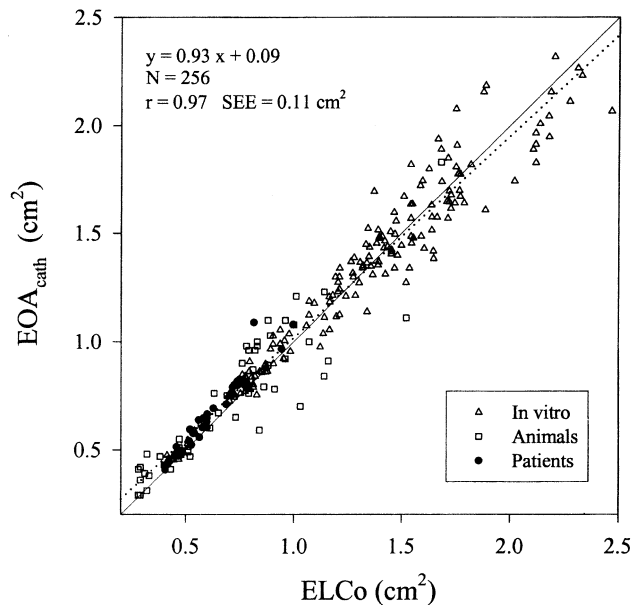


Figure 6. Relationship between aortic valve area measured by cardiac catheterization (EOA_{cath}) and energy loss (ELCO). See text. (From Garcia D, et al., ref. 11.)

Table 1. Theoretical Values of Doppler-Derived Effective Orifice Areas for Given Catheter-Derived Effective Orifice Areas and Aortic Diameters

Catheter-Derived EOA (cm ²)*	Doppler-Derived EOA (cm ²)		
	Aortic Diameter = 2.0 cm (A _A = 3.14 cm ²)	Aortic Diameter = 3.0 cm (A _A = 7.07 cm ²)	Aortic Diameter = 4.0 cm (A _A = 12.6 cm ²)
1.50 (1.69)	1.02	1.24	1.34
1.00 (1.13)	0.76	0.88	0.93
0.75 (0.85)	0.61	0.68	0.71
0.50 (0.56)	0.43	0.47	0.48

*The EOA value in parentheses was calculated from the Gorlin equation with the use of a constant of 44.3. From García D, et al., ref. 11.
EOA = effective orifice area; A_A = cross-sectional area of the aorta.

CABG than with medical therapy? (18). Answer not provided! (20).

AORTIC REGURGITATION

Natural history of rheumatic AR. A total of 75 patients with rheumatic AR were evaluated clinically every six months and had noninvasive tests at annual intervals (21); 37 patients (49%) became symptomatic within 4.6 ± 1.0 years (mean age at entry into study was 32 ± 11 years) and were scheduled for AVR within six months; one patient refused surgery, and *two died awaiting surgery*. After AVR, 10-year survival was 82% (excluding two deaths awaiting surgery). The follow-up of asymptomatic patients (mean age at entry into study was 25 ± 5 years) was 10 ± 0.4 years (Table 2).

COMMENT. Subjects in the asymptomatic group were younger at time of entry into the study. At end of follow-up, this group had large LVs and had a decline in LVEF (Table 2). It is likely they may soon become symptomatic and/or develop LV dysfunction. An important finding was the time from carditis to symptoms, about 30 years.

MITRAL STENOSIS (MS)

Mitral valve area and dobutamine. The CO by echocardiography/Doppler was used to separate patients with MS who increased CO with dobutamine by $\geq 50\%$ (group I: n =

27) and by $<50\%$ (group II: n = 30). The MVA by planimetry increased by $10.6 \pm 2\%$ ($p < 0.0001$) in group I patients and by $10.7 \pm 3\%$ ($p = 0.0035$) in group II patients. Increases in MVA by pressure half-time were much larger (22). The investigators concluded that planimetry of MVA by echocardiography/Doppler was independent of variations in flow.

Functional tricuspid regurgitation (TR) often resolves after catheter balloon commissurotomy (CBC) for MS. Seventy-one of 265 patients who underwent CBC for MS had moderate to severe TR. Up to 29 months follow-up showed TR was resolved in 1/15 patients (6.7%) of those with unsuccessful long-term CBC result but was resolved in 22/56 patients (39%) of those with successful long-term CBC result ($p < 0.05$) (23).

Cardiac events are common in pregnant women with rheumatic MS. Seventy-seven percent of 74 women who had 80 pregnancies were non-Caucasians in this study (24); 35% of pregnancies were associated with maternal cardiac complications; and fetal and/or neonatal events occurred in 30%. Multivariate independent predictors of an event were moderate or severe MS with odds ratio (OR) of 3.4 (1.2 to 10.0) and history of cardiac events before pregnancy with OR of 6.8 (1.8 to 25.9).

Open mitral commissurotomy (OMC) as alternative to CBC. A total of 276 symptomatic patients with a mean age of 30 years, MVA 0.52 cm^2 , underwent OMC instead of

Table 2. Data on Asymptomatic Patients With Rheumatic Aortic Regurgitation

	Remained Asymptomatic	Became Symptomatic	
No. of patients	138	37	
Rheumatic etiology	94%	91%	
Age at diagnosis (yrs)*	5.8 ± 4.4	5.8 ± 2.1	
Age at entry into study (yrs)	25 ± 5	32 ± 11	$p = 0.001$
Duration of follow-up (yrs)	10 ± 0.4	4.6 ± 1.0	
LVEDD (mm) baseline	69 ± 9	76 ± 9	$p < 0.05$
Final	71 ± 6		
LVEDD (mm) baseline	45 ± 5	51 ± 8	$p < 0.05$
Final	48 ± 4		
LVEF (Baseline)	0.64 ± 0.05	0.60 ± 0.05	
LVEF (Final)	0.59 ± 0.06		

*Whether due to rheumatic carditis or to aortic regurgitation is not stated. $\dagger p < 0.05$ versus baseline. Adapted from Tarasoutchi F, et al., ref. 21.

LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-systolic diameter.

CBC because of contraindications to or failed CBC (25). At 30 days there were no early deaths in isolated OMC; three patients needed reoperation. At hospital discharge, MVA was $2.6 \pm 0.6 \text{ cm}^2$. At 130 months there were no late deaths; five patients needed reoperation, and 91.6% were in NYHA functional class I or II. In operative survivors, freedom from "mitral valve failure" at 10 years was 87.0%. In patients with isolated OMC, the thromboembolism rate was 0.5% per patient-year. The CBC procedure is the procedure of first choice for severe MS if the score of the MV is low, there is no thrombus in the LA, MR is absent or is $\leq 2/4$ in severity, and commissural calcium is absent or is restricted to one commissure (26). In two studies, patients who had a "good" immediate result, the 7- and 10-year event-free survival was, respectively, $90 \pm 6\%$ and $61 \pm 5\%$ (26). If CBC is not available, OMC is the procedure of choice.

MITRAL REGURGITATION

Myocardial proinflammatory cytokine expression.

Plasma tumor necrosis factor- α (TNF- α) and its receptors were measured in patients with MR before and after MV repair (MV_{rep}). The main findings were: "1) TNF- α expression is increased both in the myocardium and plasma of patients with chronic MR; 2) there is a relationship between the extent of LV dilatation and TNF- α expression; 3) correction of the LV volume overload state with MV repair leads to reversal of TNF- α expression; and 4) the extent of regression in the LV remodeling, i.e., reverse LV remodeling after MV_{rep}, is proportionate to the amount of preoperative TNF- α expression" (27).

Plasma natriuretic peptide (NP) levels are elevated in MR. Atrial and brain plasma natriuretic peptides (ANP and BNP) were measured in 49 patients with MR (28). The NPs rose with increasing severity of MR and increases of LA dimensions ($p < 0.001$). The NPs in symptomatic patients were greater than in asymptomatic patients ($p < 0.001$) and greater in asymptomatic patients with MR than in normal controls ($p < 0.0001$); NPs did not correlate with LV dimensions or LVEF.

The sympathetic nervous system is activated in MR. Calculated extravascular norepinephrine release rates (NE₂) were greater in patients with MR than in controls ($p = 0.007$) (29). The NE₂ levels were increased in patients with MR who were in clinical class I ($p = 0.05$), or had a mean PA wedge pressure $< 12 \text{ mm Hg}$ ($p = 0.05$), or had LVEF ≥ 0.60 ($p = 0.06$). Mean NE₂ values were increased further in patients who had an LVEF < 0.60 ($p = 0.02$).

ACE inhibitor and beta-blockers in experimental MR. Mitral regurgitation was created in 11 closed-chest dogs (30). Both MR and LV were assessed at three, six, and nine months. Lisinopril 20 mg/day was started at three months and given for the next six months (i.e., until end of study); atenolol up to 100 mg/day was added at six months and was given for the next three months. Atenolol had a beneficial

effect on MR, LV forward stroke volume, and on LV end-systolic stiffness constant (an index of myocardial contractility); these effects were not seen with lisinopril. Lisinopril reduced LV end-diastolic pressure and PA wedge pressure; the addition of atenolol brought about further reductions in both of these parameters.

COMMENT. Previous experimental studies of MR have failed to show an increase of ACE activity in the myocardium and the peripheral vessels (31,32); also, ACE inhibitor therapy did not reduce MR (30,31). Note that the previously cited study (30) documented increased levels of NE₂ in patients with MR.

Timing of surgery in MR. Otto (33) has highlighted several controversial issues. She stated:

- Mitral valve surgery based on Doppler criteria alone is *not* appropriate.
- Utility and timing of surgery for secondary MR remains controversial.
- In patients with MR and atrial fibrillation, concurrent atrial procedure to restore sinus rhythm likely will become used more widely and likely will be a standard adjunct to MV_{rep} in the future.
- In patients with severe MR and LVEF < 0.30 or end-systolic dimension $> 55 \text{ mm}$, surgery should only be considered if it is highly likely that MV_{rep} can be performed.

MITRAL VALVE REPAIR

Long-term follow-up in nonrheumatic and rheumatic MR.

Carpentier's techniques were used in the first 162 patients who underwent MV_{rep} between 1970 and 1994, 90% of whom had "degenerative" MV. Patients had a mean age of 56 years; NYHA functional class II or III was present in 91% (34). Operative mortality was 1.9%. The median follow-up was 17 years (range, 1 to 29 years); all patients except one were in NYHA functional class I and II. Survival, cardiac event-free survival, and reoperation rates are shown in Figure 7.

From 1970 to 1994, a total of 951 patients with rheumatic MR were operated on with reconstructive techniques elaborated by Carpentier. Mean age was 25.8 years; sinus rhythm was present in 63%. Operative mortality was 2%. Mean follow-up was 12 years (maximum, 29 years). Survival and reoperation rates are shown in Figure 8 (35).

COMMENT. Although MV_{rep} had been performed in the 1950s and 1960s (36), current MV_{rep} techniques and enthusiasm had their foundation as very good operative procedures when described by Alain Carpentier in the early 1970s (37,38). The above two studies present excellent outcome data of MV_{rep} by Carpentier that dates back to 1970.

Mitral valve repair for MR in the United States. The Society of Thoracic Surgeons National Cardiac Database

Mitral Valve Repair for MR

"Isolated" Non-Rheumatic; Age: 56 ± 10 yrs

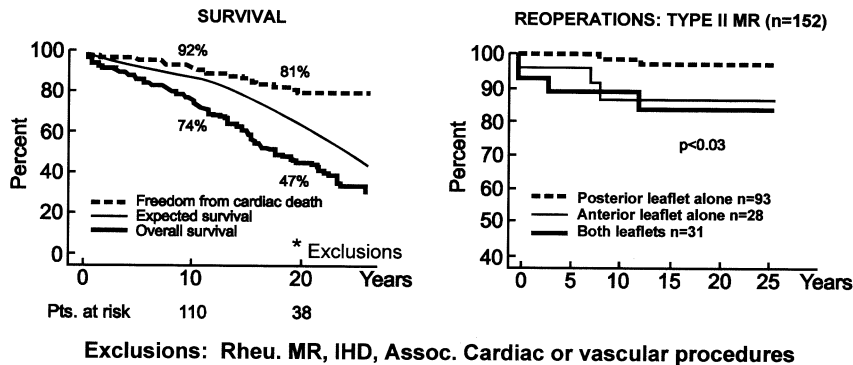


Figure 7. Survival at 10 and 20 years and freedom from cardiac death (left panel). Reoperations according to leaflet prolapse (right panel). MR = mitral regurgitation. (From Braumberger E, et al., ref. 34.)

shows that the performance of MV_{rep} in 1990 was 23.2% and in 1999 had increased to 32.0%, $p < 0.0001$ (39).

The proportion of patients undergoing MV_{rep} in 1999 and 2000 (39) decreased with age (41.2% in patients 20 to 39 years, 36.1% in patients >70 years, $p = 0.0016$). The MV_{rep} was performed more commonly in males (43.5%) than in females (32.0%), $p < 0.0001$, less commonly as NYHA functional class increased (class I, 47.8% vs. class IV, 33.2%) and for emergent operative status (33.2%) versus for elective/urgent (38.5%); p value for both < 0.0001 .

The investigators concluded that the national MV_{rep} rate is low ($\leq 42.4\%$), even between 1999 and 2000 (39), and the expected rate should be at least 74%. They observed: "To approach this standard it may behoove the cardiac surgical community to adopt a more formal approach to educating surgeons in these techniques" (40).

COMMENT. In Paris, France, the incidence of MV_{rep} is $\geq 90\%$ (40). Thus, the investigators' estimate of 74% may be too low. **Recurrence of MR after MV_{rep} for MR.** A total of 242 consecutive patients underwent MV_{rep} for "degenerative dis-

ease." Hospital mortality was 1.7%. At eight years, survival was 90.9%; freedom from reoperation was 94.2%; freedom from bleeding and thromboembolic events was 90.4%. The incidence of severe MR (grade $>2/4$) was 1.7% at one month, $17.2 \pm 3.8\%$ at five years, and 28.3% at seven years. In patients without "adequate surgical techniques (chordal shortening, use of annuloplasty ring or sliding plasty)" linearized recurrence rate of severe MR was 2.5% per year (41).

The researchers concluded: "The durability of successful mitral reconstruction for degenerative mitral valve disease is not constant, and this should be taken into account when asymptomatic patients are offered early mitral valve repair" (41).

COMMENT. This was a careful long-term study containing frequent echocardiographic/Doppler studies.

PROSTHETIC HEART VALVES

Aortic valve replacement in a conscious patient. A man age 70 years with AS, no significant CAD, or hypertension

MV Repair; Rheumatic MR

Mean Age 25.8 years

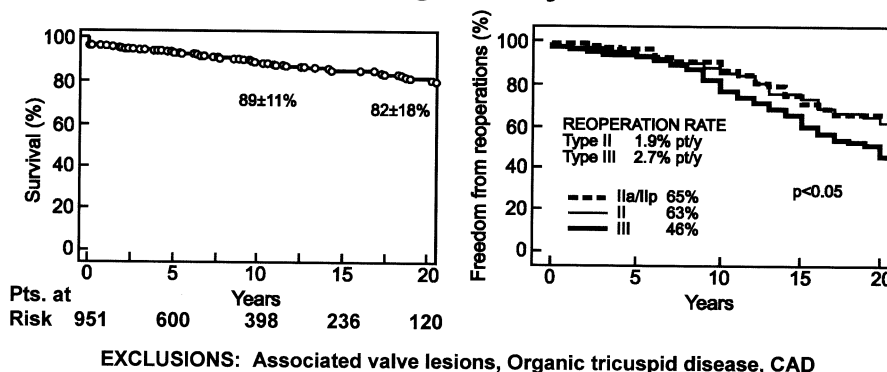


Figure 8. Actuarial survival after mitral valve (MV) repair of patients with rheumatic mitral regurgitation (MR) is shown in left panel. Freedom from reoperation after MV repair of patients with rheumatic MR is shown in right panel. (From Chauvand S, et al., ref. 35.)

Table 3. 20-Year Outcome Data From the Edinburgh Heart Valve Trial

	Aortic Valve Replacement			Mitral Valve Replacement		
	Mechanical	Porcine	p Value	Mechanical	Porcine	p Value
Survival						
All survivors	28.4 (4.4)	31.3 (4.7)	0.57	22.4 (3.8)	18.4 (3.6)	0.41
With original prosthesis	27.5 (4.3)	13.7 (3.6)	0.025	20.8 (3.7)	2.5 (1.4)	<0.0001
Without major event	15.2 (3.5)	8.1 (3.0)	0.34	11.9 (3.0)	2.5 (1.4)	0.005
Valve-related events						
Reoperation	7.4 (3.0)	56.2 (8.4)	<0.0001	13.4 (3.9)	77.6 (6.7)	<0.0001
All bleeding	61.1 (7.6)	42.4 (12.1)	0.001	53.1 (8.2)	37.2 (10.9)	0.39
Major bleeding	37.8 (7.1)	32.0 (12.6)	0.021	47.3 (8.5)	9.5 (4.1)	0.044

Adapted from Oxenham H, et al., ref. 46.

had AVR under regional anesthesia using a number of analgesic and sedative agents (42). There was no endotracheal intubation, and the postoperative course was uneventful.

Tissue-engineered heart valve (TEHV). Three studies have described efforts to develop TEHV. These consisted of reseeding in the following ways: 1) with human marrow stromal cells on the trileaflet heart valves fabricated from rapidly absorbable polymers (43); 2) cultivated human venous endothelial cells onto cadaver human allografts (homografts) that had been preserved in antibiotic-enriched Earle's medium 1999 and then decellularized (44); and 3) aortic valve interstitial cells to repopulate aortic valve leaflets that had been decellularized aortic valve leaflets (45). These constructed valves showed morphological and mechanical properties similar to human native heart valves.

COMMENT. The development of TEHV for valve replacement in humans shows promise. Imagine the possible benefits when cardiac valves are developed from human stem cells.

Edinburgh heart valve trial. A total of 541 patients were randomized from 1975 to 1979 to receive either a mechanical valve or a bioprosthesis. Their mean age was 53.9 years. The major findings at 20 years [% (\pm SEM)] are shown in Table 3 (46). There were no statistically significant differences for all embolism, major embolism, or endocarditis events. The investigators concluded: "Survival with an intact valve is better among patients with the Bjork-Shiley spherical tilting disc prosthesis than with a porcine prosthesis but there is an attendant increased risk of bleeding."

COMMENT. The only other "large" randomized trial of a mechanical valve versus the porcine valve was the Department of Veterans Affairs (DVA) trial (47) in which the follow-up was 18 years (average, 15 years). The major differences between the two trials are: 1) in the Edinburgh study, the patients were younger and there were more patients undergoing MVR; 2) in the DVA trial, after AVR at 15 years the survival was better with a mechanical valve than with a bioprosthesis (79% vs. 66%, $p = 0.02$); the DVA trial had 87% more patients undergoing isolated AVR; 3) the bleeding rate in the DVA trial was higher because the patients were more heavily anticoagulated; and 4) both trials included rates of all bleeding, but in the

Edinburgh trial minor bleeding was not recorded for the first five years of the study.

Prosthetic heart valve thrombosis (PHVT). A single-center study reported on 110 consecutive patients presenting with 127 instances of PHVT between 1978 and 2001 and who received fibrinolytic therapy (FT) (48). Full success was obtained in 90/127 instances (70.9%); of 90 instances of full success, 62 (69%) were with a single fibrinolytic agent; multiple FTs resulted in complete success in another 17% and failure in 12%. Streptokinase and rt-PA fared better than urokinase. Complications occurred in 32 patients (25.2%) (48–50).

The investigators concluded: "FT is effective in most cases of PHVT, regardless of prosthesis or site involved. However, embolism, hemorrhage, and death were not uncommon after lytic therapy of left-sided PHVT, limiting its application to patients at high risk with alternative therapy" (48).

COMMENT. Thrombosis of PHV is an uncommon but important complication because it can be life-threatening. The cited study (48) is a large and important one. Problems in analysis of results of FT are: 1) patients who initially had surgery are *excluded*; 2) patients who are in NYHA functional class I or II have better results than those in class III or class IV whether patients are treated with surgery or FT; and 3) in patients with pannus only or pannus with thrombus (estimated incidences of 10% and 40%, respectively), it is not likely that FT alone will be successful (Fig. 9). Review of previously reported operative mortality of surgery for PHVT ranged from 10% to 60% (Table 4). Therapeutic suggestions are shown in Table 5.

Results of PHV in nonagenarians. Two studies reported the results of PHV in nonagenarians. Thirty-five nonagenarian patients (aged 90 to <100 years old) had PHV between 1986 and 2000 and are registered in the UK Heart Valve Registry. The mean age was 91 ± 1.3 years, and 30-day mortality was 17.1%. The two-year survival was 74.3% (women 77.8%, men 70.6%) (51). Twenty-one patients (AVR in 5; valve + CABG in 16) had PHV surgery from 1993 to 2002; their mean age was 91.4 years. There was no operative mortality. At a mean of 2.53 years (range, 0.16 to 7.1 years) after PHV the survival was 81% (52).

COMMENT. In 2000, nonagenarians in the United States totaled 1.6 million, and centenarians numbered 72,000; by

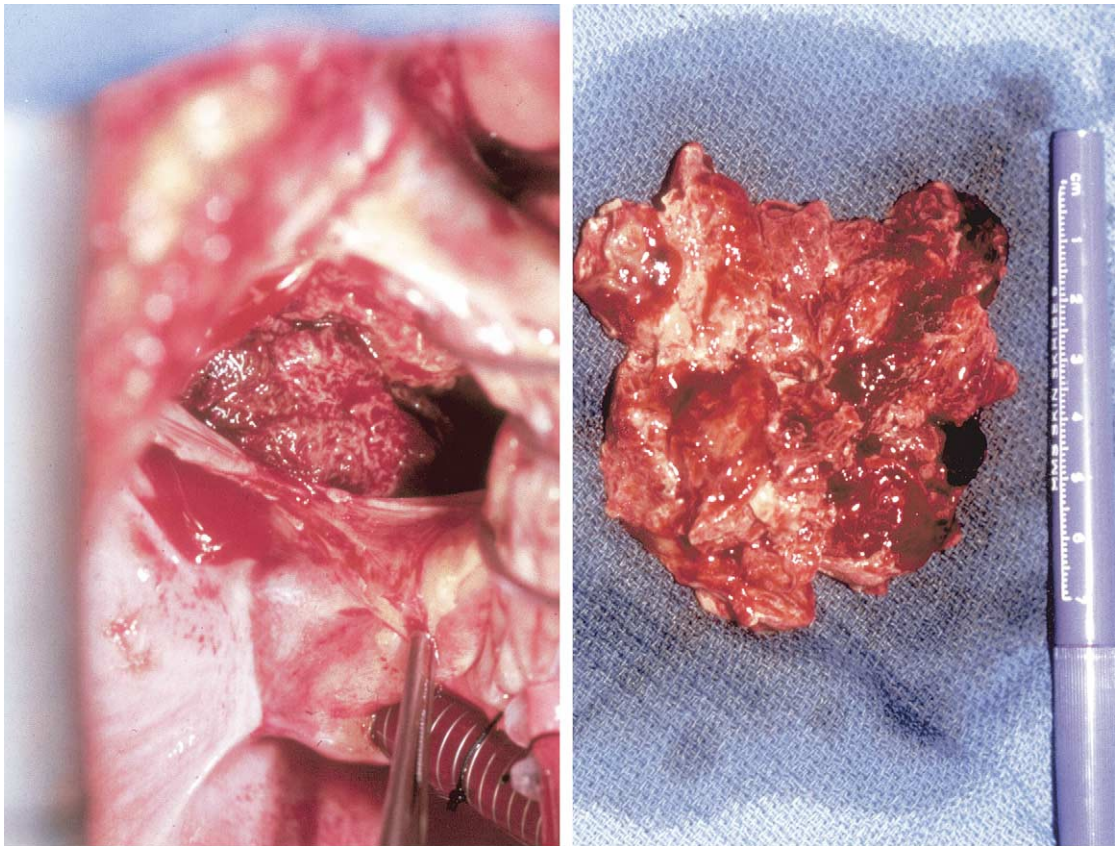


Figure 9. Thrombosed mitral valve in patient in New York Heart Association functional class IV. View from left atrium shows thrombus on a valve with pannus (**left panel**); the removed thrombus is shown in the **right panel**. Patient had replacement of the thrombosed valve and is doing well. Figures provided by Dr. Ismael Nuno, LAC + USC Medical Center, Los Angeles, CA.

2050, the corresponding numbers are expected to be 8.8 million and 1.1 million, respectively (52).

Patient outcomes with the “small” Carpentier-Edwards pericardial valve. A total of 94 patients were ≥ 75 years of age; 28/94 (30%) were women. Valve areas at 14 ± 3.2 months’ postoperation are shown in Table 6 (53).

Operative mortality was 6.3% and late (12-year) mortality was an additional 17.2%.

COMMENT. Valve areas cannot be measured with any degree of accuracy to hundredths of a centimeter; thus, the calculated valve areas should be rounded to the first decimal; the satisfactory long-term survival of 82.8% (excluding

operative mortality) in patients age ≥ 75 years at the time of PHV was probably because most had mild or moderate valve prosthesis–patient mismatch; and an earlier study had shown that patients who received a “small” PHV and had a normal LVEF had similar exercise capacity as age- and gender-matched controls (54).

Table 4. Thrombosed Prosthetic Heart Valve

Mortality with surgery: 10% to 60%
Factors contributing to high mortality:
● NYHA functional classes III or IV and duration in that class
● Severe co-morbid conditions:
Severe clinical heart failure
Severe LV dysfunction
Pulmonary edema
Pulmonary arterial and right atrial hypertension
Very low cardiac output
Multisystem organ failure (renal, hepatic, pulmonary, CNS, and blood)

LV = left ventricular; NYHA = New York Heart Association.

Table 5. Therapeutic Strategies for Prosthetic Heart Valve Thrombosis

Right-sided PHVT
FT is first choice of therapy. If successful, it should be followed by IV heparin + warfarin until INR appropriate, followed by warfarin plus low-dose aspirin.
If FT is unsuccessful, surgery.
Left-sided PHVT
● Surgery is first choice for:
pannus and pannus plus thrombus
“large thrombus”
patients in NYHA classes III/IV
unsuccessful FT
● FT is first choice for:
“small” thrombus
patients in NYHA classes I/II
those with severe co-morbid conditions (Table 4)
if surgery is not a viable option

FT = fibrinolytic therapy; NYHA = New York Heart Association; PHVT = prosthetic heart valve thrombosis.

Table 6. AVA of “Small” Carpentier-Edwards Pericardial PHV in Patients Aged ≥ 75 Years of Age

PHV Size	n	BSA (m ²)	AVA (cm ²)	AVA Index (cm ² /m ²)
19 mm	17	1.65 \pm 2.0	1.27 \pm 0.07	0.78 \pm 0.08
21 mm	25	1.69 \pm 1.4	1.48 \pm 0.03	0.88 \pm 0.08

From Vitale N, et al., ref. 53.

AVA = aortic valve (area); BSA = body surface area; PHV = prosthetic heart valve.

Dialysis and valve replacement. 1) The STS National Cardiac Surgery Database (55) shows that in patients on dialysis the operative mortality for PHV is high (Table 7). 2) The Renal Dialysis Database (56) showed that in 5,858 patients undergoing PHV the later mortality is very high (Table 7). These investigators concluded: “There is no significant difference in survival of dialysis patients after cardiac valve replacement in tissue versus non-tissue valves. Current practice guidelines proscribing the use of bioprosthetic heart valves in hemodialysis patients should be rescinded.”

COMMENT. Actually the ACC/AHA Guidelines give bioprostheses a class II and *not* a class III recommendation (57). The important issues are the high operative mortality and the very high “early” subsequent mortality. The cause(s) of mortality was not provided. In patients with less renal failure the survival is likely to be better; therefore, the rate of structural valve deterioration (SVD) would be expected to be much higher with use of bioprostheses.

Cryopreserved homografts in isolated AVR. Over a period of 9.25 years, 164 of 955 (17%) patients undergoing AVR had homograft AVR; 64 patients were excluded because of various reasons including need for predetermined CABG (58). Of the remaining 100 patients, 24 were aged < 40 years, and 70 were aged 40 to 65 years. Twelve- and 60-month survival rates were 100% and 98%, respectively; 45 patients had postoperative morbidity, which included 6

Table 7. Valve Replacement in Patients on Renal Dialysis

STS National Cardiac Surgery Database*

Operative Mortality:*

AVR	17.07%
MVR	22.45%
AVR + CABG	24.59%
MVR + CABG	36.89%

U.S. Renal Dialysis Database†

Mortality

	Whole Group	Tissue Valve	Nontissue Valve
1 yr	46.0 \pm 1.3%	45.3 \pm 3.4%	46.0 \pm 1.4%
2 yrs	60.4 \pm 1.3%	60.3 \pm 3.5%	60.3 \pm 1.4%
3 yrs	71.9 \pm 1.3%	73.8 \pm 3.5%	72.8 \pm 1.4%
5 yrs	85.2 \pm 1.3%	86.2 \pm 3.4%	85.1 \pm 1.3%
10 yrs	95.6 \pm 1.3%	95.6 \pm 3.1%	95.7 \pm 1.1%

*Adapted from Edwards FH, et al., ref. (55). †Adapted from Herzog CA, et al., ref. (56).

AVR = aortic valve replacement; CABG = coronary artery bypass graft; MVR = mitral valve replacement.

(6%) with acute myocardial infarction, 1 with cardiac arrest, and 2 with strokes. Homograft valve-related event rate was 4.6% (95% CI, 1.2% to 10.8%) at one year and 5.3% (2% to 13.8%) at five years. The investigators concluded that “given the superior durability in younger patients, this may be the AVR prosthesis of choice for the young (< 40 years) to middle-aged (40 to 65 years) patient who cannot commit to life-long anticoagulation” (58).

COMMENT. The study represented a selected series. The reported incidence of acute myocardial infarction in those without CAD of 6% was high; follow-up was too short to determine incidence of SVD, and there were no serial echocardiographic/Doppler studies to detect SVD. *Note:* 1) homografts are more difficult to insert; need reimplantation of coronary arteries; 2) they may have a “high” incidence of perioperative myocardial infarction (58); 3) the incidence of SVD is quite high on longer-term follow-up (59–61); 4) the SVD deterioration rate is similar to that of bioprostheses

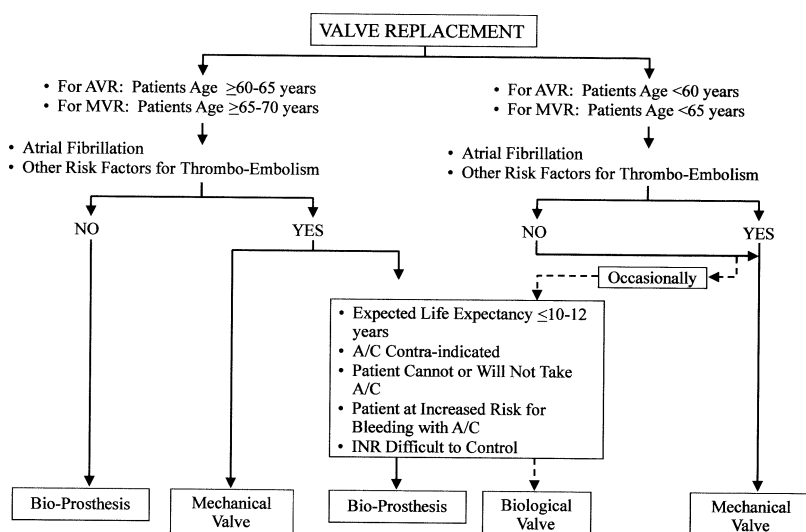


Figure 10. Choice of prosthetic heart valve in adult patient. (From Rahimtoola SH, ref. 61.)

(61,62); and 5) homografts are more expensive than are bioprostheses!

Choice of PHV for adult patients. The choice of PHV based on age is shown in Figure 10 (61). However, exceptions exist to this general rule. The choice of a PHV should be based on several factors, including known long-term results from randomized trials and databases, patient characteristics such as age, associated cardiovascular, and other co-morbid conditions; expected survival of the patient based on age and gender, associated cardiovascular and co-morbid conditions, and known outcomes; unique patient needs; complete and accurate discussion and information of all of the above with the patient; and joint decision with patient, cardiologist, and cardiac surgeon.

PHVs and pregnancy. In patients with mechanical PHVs, the incidence of warfarin embryopathy is low (average 3.9%) with use of a regimen of intravenous unfractionated heparin in the first three months (especially between the 6th and 12th week) of pregnancy, and warfarin from week 13 to the last two weeks of pregnancy when intravenous unfractionated heparin is again used. Ten studies comprising 427 pregnancies reported the incidence was zero; four recent studies from 1994 to 1999 reported an incidence of 3/189 (1.6%) of live births (62).

Subcutaneous heparin does not improve fetal outcome and does increase maternal mortality. The U.S. Food and Drug Administration (FDA) has issued warnings about the use of low-molecular-weight heparin during pregnancy.

Pregnancy in women with bioprostheses is associated with SVD; the incidence may average 24% during or shortly after pregnancy. After bioprosthetic PHV, the incidence of SVD at 10 years was 55% to 76%; the incidence of PHV-related reoperation was 60% to 80%; the mortality rate for reoperation was 3.8% to 8.7%.

Algorithms for management of young women with valvular heart disease (VHD), those who need PHV, and of young women with PHV who become pregnant have been developed (62).

MISCELLANEOUS

Drug-related VHD. Pritchett et al. (63) reported three patients taking pergolide mesylate (Permax, Eli Lilly and Company, Indianapolis, Indiana), an ergot-derived dopamine receptor agonist used to treat Parkinson disease and restless leg syndrome. The patients developed valvular lesions that were strikingly similar to those previously reported by Connolly et al. (64) in patients taking anorectic drugs fenfluramine and dexfenfluramine.

Reversal of excessive anticoagulation. Novo Seven (Novo Nordisk, Princeton, New Jersey) is a genetically engineered concentrate of human coagulation FV-IIa, which is structurally similar to native human plasma-derived FV-IIa. Thirteen patients (only two with VHD) with critically

“increased INRs” requiring immediate reversal of warfarin-induced anticoagulation were given rFV-IIa in doses as low as 15 to 20 mg/kg intravenously over 3 to 5 min (65). The INR was immediately reduced after a single infusion. There were no adverse effects.

Robotic surgery. As part of an FDA trial, MV_{rep} was performed in 38 patients using the robotic daVinci surgical system (Intuitive Surgical, Mountain View, California) (66). There were no “operative deaths,” strokes, or device-related complications; one patient died at 20 days. One patient required MVR for hemolysis and one was re-explored for bleeding.

Pre-existing VHD in patients with acute coronary syndrome. In the Euro Heart Survey of acute coronary syndrome (67), of 10,207 patients with data on VHD, 489 (4.8%) had a diagnosis of pre-existing VHD, of whom 54.0% had moderate/severe MR and 31.7% had moderate/severe AS. Patients with pre-existing VHD had worse baseline clinical co-morbid conditions and had a more complicated in-hospital course. Their OR for adjusted in-hospital mortality risk ranged from 1.55 to 1.92 depending on the type of ACS.

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